

SYNTEX CALIFORNIA

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Dr. Ernst Sorkin
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Dear Ernst:

Thank you for your letter of August 9th. I would like to be able to answer your questions about Syntex more decisively but it is difficult for me to speak for the Company and I can only give you my own impressions of it from the outside.

As to the overall direction of the Company, this at least ought to be no great concern. It is certainly true that there were many changes in the earlier days of its development but at the present time Syntex is a publically owned corporation whose stock is listed on the American Stock Exchange and the shares of which are quite widely distributed. This means, in practice, that the present management could only be displaced by the most unexpected and sinister events and, particularly in view of the great success of the present corporate policy, I do not believe that there should be any cause for concern in this direction. As to the stability of the program, I believe you are quite right to bring up the point. My own considered view is that on a five-year basis at least, there should be no cause for concern. The directors are very well aware of the long term requirements before basic research can be translated even in part into practical and useful developments. In fact, what is unique about the present venture, is the dedication to a long-term point of view on the part of the company and it is in hopes of setting a rather unique pattern in pharmaceutical research that I have been interested in the affiliation myself. Realistically, if after the first five years of work, the Institute had done nothing that could even point to the possibility of a pharmaceutical development, I can visualize that the directors might begin to wonder about the wisdom of their commitment. However, even in this event, I believe that the Institute would have obvious value to Syntex -- from the standpoint of its overall prestige and, in addition, by merely having some intelligent people doing pioneering research work who might instill some general interest in the overall Syntex program. Since the whole strength of the Company has depended upon its research, I cannot conceive of any fundamental retreat from a basic research policy but I might have to admit with you that there would be some risk of a dampening of enthusiasm over a long period of time. However, the time interval that would be appropriate for this discussion would be, in my opinion, five years and not one. If the experiment failed from the standpoint of ultimate pharmaceutical productivity, I would visualize that the Institute might be converted into a self-sustaining, non-profit foundation, of which there are already many examples and which would have no difficulty in obtaining continued support if it indeed had already established the basic facilities for doing its research work. I do not seriously envisage that this would happen, but I mention it as an indication of the kind of security that is available against the calculable risks. By and large, I can honestly recommend to you that these particular issues should be no cause for concern on your part. There are, of course, other questions that I imagine you will be considering very seriously.

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The matters of budget and facilities, etc. should not be so difficult to decide and will doubtless be the subject of further correspondence, particularly if you indicate that your interest is sustained.

Perhaps most important is whether you are sympathetic to the basic premises of the intended organization. In the long run, will work in the fields and at the level in which you are interested justify the Company's continued support? Can this be accomplished without unduly distracting you from your own basic scientific objectives? If I did not believe in the possibility of a reasoned affirmative answer, I would not have proposed the arrangement in the first place. However, what the answer actually should be is something you will ultimately have to work out for yourself. What I have in mind is that in the course of your basic work, and to some extent in consequence of it, possibilities of useful applications will present themselves. It will be your own responsibility to evaluate these possibilities and to arrange the means to bring them to fruition. This would imply that over the course of time a considerable supporting staff should be developed at the Institute in order to follow through on these conceptions. Fortunately, the contract with Lilly also provides access to their very large scale facilities for routine screening in a number of areas and this should greatly relieve the burden of testing that might otherwise be incumbent on the Syntex laboratory. In any position, not least in the University, there are many obligations to the institution besides one's own research -- for example, teaching and administration. I would visualize that in the Institute your responsibilities towards ultimate application would be the equivalent of these other tasks in a university position.

You asked about your colleagues -- a very important question. The initial research group, as you must already know, would consist of five investigators (hopefully including yourself). Of these, two are already chosen at the present time: Boris Rotman and John Zderic. Rotman is an accomplished biochemist and microbiologist. His main interests at the Institute would be the mechanism by which nucleic acids enter bacteria and other cells. This is, of course, a problem of very great interest to us in connection with DNA transfer and genetic transformations. Zderic is an organic chemist from Syntex Laboratories in Mexico who is switching fields now from steroids to nucleotides. All I can say of him is that Djerassi thinks very highly of him as a chemist. In addition, Zderic would furnish the administration liaison between the Institute and Syntex Corporation. The other two positions are not yet filled. One has been offered to Dr. W. E. Razzell who has spent some years with Khorana at British Columbia and is still there at the present time. His main interest is in the organic chemistry and biochemistry of polynucleotides -- you will see examples of his work in the JBC for August, 1959 and JACS 79, 1002, 1957. He is particularly interested in methods for sequence analysis of DNA and in the preparation of synthetic polynucleotides.

I hope this discussion can help answer some of your questions and please write me again if I can further clarify any of these or other issues.

You remarked about Szilard's papers on antibody formation. He presents a rather formalistic model, perhaps over-elaborately, which I cannot take too seriously. Fitting it into my own approach to the problem, he seems to be suggesting that each cell of the antibody-forming series contains all the information necessary to produce any conceivable antibody. He has then given a somewhat detailed analysis of the way in which the kinetics of antibody synthesis could be arranged so that it would follow an on-off pattern. I have no quarrel with the latter part of this, although I am not sure of the necessity of worrying about this aspect of the problem at the present time. I am not even as optimistic as Szilard is in limiting the variety of potential antibodies to the point of comfort in assigning a separate preformed genetic determinant in each cell for each antibody. On the other hand, I think the idea of looking for a generalized repressor -- which

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is not Szilard's, he is thinking of specific ones -- is not at all a bad one and it would be important to have the datum as to whether or not such repressive effects actually exist. Your answer to this is presumably no.

Trusting I will hear further from you, as ever

Joshua Lederberg

JL/jh